CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

IRON ISOMALTOSIDE 1000 (MONOFERRIC)

(Pharmacosmos A/S)

Indication: For the treatment of iron deficiency anemia in adult patients who have intolerance or unresponsiveness to oral iron therapy.

Service Line:	CADTH Common Drug Review
Version:	Final
Publication Date:	May 2020
Report Length:	29 Pages

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

AE	adverse event
CBC	complete blood count
CDR	CADTH Common Drug Review
CKD	chronic kidney disease
CUA	cost-utility analysis
Hb	hemoglobin
HR	hazard ratio
IDA	iron deficiency anemia
QALY	quality-adjusted life-year

Table 1: Summary of the Sponsor's Economic Submission

Drug product	Iron isomaltoside 1000 (Monoferric)
Study question	What is the cost-effectiveness of iron isomaltoside 1000 for the treatment of patients with IDA who are intolerant or unresponsive to oral iron therapy?
Type of economic evaluation	Cost-utility analysis
Target population	Adult patients with IDA who have an intolerance or unresponsiveness to oral iron therapy
Treatment	IV iron isomaltoside 1000
Outcome	QALYs
Comparator	IV iron sucrose (Venofer)
Perspective	Canadian publicly funded health care payer
Time horizon	6 months
Results for base case	Iron isomaltoside 1000 was dominant, costing $569.51 less than iron sucrose when administration costs were included, and associated with 0.0026 more QALYs
Key limitations	• The long-term cost-effectiveness is unknown — all clinical inputs and costs occur in the first 5 weeks of the model. • The health states, which are based on achieving or not achieving a response as defined by an improvement of at least 2 g/dL in hemoglobin levels, are of uncertain relevance. • The number of iron sucrose infusions was overestimated for Canadian practice. • The generalizability of the disutility values for patients with IDA in Canada is uncertain. • The chronic use of IV iron supplementation was not considered. • Monitoring costs, particularly for iron sucrose, were overestimated. • Adverse events were not considered. • Most probabilistic variations within the model (including nurses' wages) were based on assumptions.
CADTH estimate(s)	• In the CADTH reanalysis, it was assumed that laboratory monitoring tests are equal between comparators, with 2 tests per patient. CADTH also assumed that 300 mg of iron sucrose is infused per visit, reducing the mean number of infusions for iron sucrose from 6 to 4. Additionally, CADTH used limits for the hourly wage for nurses based on the minimum and maximum entries for Canada as cited by Statistics Canada. • In the CADTH base case, iron isomaltoside 1000 was dominant, costing $148.42 less than iron sucrose when administration costs were included, and associated with 0.0026 more QALYs.

IDA = iron deficiency anemia; QALY = quality-adjusted life-year.

Drug	Iron isomaltoside 1000 (Monoferric)
Indication	For the treatment of iron deficiency anemia in adult patients (≥ 18 years of age) who have an intolerance or unresponsiveness to oral iron. The diagnosis must be based on laboratory tests.
Reimbursement request	As per indication.
Dosage form(s) and route of administration) and strength(s)	100 mg/mL administered intravenously
NOC date	June 22, 2018
Sponsor	Pharmacosmos A/S

Executive Summary

Background

Iron isomaltoside 1000 (Monoferric), also known as ferric derisomaltose, consists of iron and isomaltoside, a carbohydrate, forming a matrix structure designed for the controlled release of iron in the body. Iron isomaltoside 1000 is indicated for the treatment of iron deficiency anemia (IDA) in adult patients who have intolerance or unresponsiveness to oral iron therapy. The diagnosis must be based on laboratory tests. It is available as 100 mg/mL of elemental iron in 1 mL, 5 mL, and 10 mL vial sizes, at submitted prices of $45, $225, and $450, respectively, or $45 per mL.

Iron isomaltoside 1000 can be dosed in one of two ways: first, by using the Ganzoni formula, accounting for individual patient weight, assumed iron stores, and target and actual hemoglobin (Hb) levels; or, second, according to a simplified dosing table leading to doses of 1,000 mg, 1,500 mg, or 2,000 mg (see Table 4). As a bolus injection, up to 500 mg of iron isomaltoside 1000 may be administered up to once weekly at a rate of 250 mg per minute. As an infusion, if the cumulative required iron dose exceeds 20 mg iron/kg body weight, the dose should be split into two administrations given at least a week apart. Single doses above 1,500 mg are not recommended. Using the simplified table, the drug acquisition cost per course of therapy is $450 to $900.

The sponsor submitted a cost-utility analysis (CUA) comparing iron isomaltoside 1000 to iron sucrose (Venofer) for adults with IDA who have intolerance or unresponsiveness to oral iron therapy, from the perspective of a Canadian publicly funded health care system over a six-month time horizon. Patients entered the model in the IDA health state and, at the end of the first week, transitioned into either a responder or a nonresponder health state. Patients could become responders during any of the first five weeks. The efficacy of iron sucrose, in terms of the proportion of patients who had responded to treatment in each of the first five weeks of the model, was based on the percentage of patients with an Hb increase of 2 g/dL or more in the iron sucrose group of the PROVIDE trial.[1] Relative response in the iron isomaltoside 1000 group was estimated using a hazard ratio (HR) of 2.488 over the first five weeks as reported in PROVIDE.

The utility values for patients in the responder health state was assumed to be 0.863, the average Canadian utility value.[2] Nonresponders were assigned a utility of 0.713, based on a disutility of 0.15 reported in US patients with anemia.[3] From week 6 onward, all patients in

the model were assigned the utility value of responders, but without further treatment costs (e.g., no re-treatment). Cost inputs included the acquisition cost of iron therapy based on the mean received dose for each comparator in the PROVIDE trial. The number of infusions required was calculated by dividing the mean dose by the maximum dose per treatment (i.e., 1,000 mg and 200 mg for iron isomaltoside 1000 and iron sucrose, respectively). Additional costs included those associated with drug administration.

The sponsor reported that iron isomaltoside 1000 was associated with cost savings of $570 compared to iron sucrose and 0.0026 additional quality-adjusted life-years (QALYs). Iron isomaltoside 1000 was dominant over iron sucrose.

Summary of Identified Limitations and Key Results

The CADTH Common Drug Review (CDR) identified a number of limitations in the model submitted by the sponsor. The health states, based on response (an Hb increase of ≥ 2 g/dL) as opposed to the absolute Hb level, were of uncertain relevance in terms of their relationship to utility values. The number of infusions required for the comparator, iron sucrose, is likely overestimated compared to clinical practice, along with the number of monitoring tests required. While the analysis is probabilistic, the majority of inputs relied on assumed variances rather than being informed by data; as a result, it is unclear whether uncertainty has been appropriately characterized in the model. The impact of adverse events (AEs) associated with iron isomaltoside 1000 and iron sucrose administration was not considered, increasing uncertainty in the very small quality of life difference found between them. Additionally, the long-term cost-effectiveness of iron isomaltoside is uncertain.

CADTH reanalyses considered the number of iron sucrose infusions consistent with a 300 mg dose being administered at a time, an equal number of laboratory tests for each comparator, and the introduction of data-informed variance for nursing wages.

Conclusions

In CADTH's base case, iron isomaltoside 1000 was associated with 0.0026 additional QALYs and savings of $148; thus, iron isomaltoside 1000 remained dominant over iron sucrose. Sensitivity analyses explored the impact of varying the disutility associated with IDA and with assuming no difference in efficacy between comparators. Iron isomaltoside 1000 remained cost saving in each scenario when total costs were included, although it is more expensive than iron sucrose when only drug costs are considered.

A number of limitations could not be addressed, including uncertainty in the relevance of the health states as modelled, the lack of consideration for AEs, the assumed variation in the probabilistic inputs, and the unknown long-term cost-effectiveness of iron isomaltoside 1000 compared to iron sucrose.

Information on the Pharmacoeconomic Submission

Summary of the Sponsor's Pharmacoeconomic Submission

The sponsor submitted a CUA comparing iron isomaltoside 1000 (Monoferric) to iron sucrose (Venofer) for the treatment of adult patients with IDA who have intolerance or unresponsiveness to oral iron therapy. The base case was a probabilistic model of 5,000 iterations over a six-month time horizon. No discounts were applied to costs or outcomes, nor was mortality applied, given the short time horizon. Patients entered the model in the IDA health state and, at the end of the first week, transitioned into either a responder health state or a nonresponder health state. Thereafter, responder patients remained in the responder state while nonresponders either remained nonresponders or switched to the responder state at the end of each of the first five weeks (see Figure 1).

The efficacy of iron sucrose, in terms of the proportion of patients who had responded to treatment in each of the first five weeks of the model, was based on the percentage of patients with an Hb increase of 2 g/dL or more in the iron sucrose group of the PROVIDE trial, as reported in a Kaplan–Meier curve.[1] PROVIDE was an open-label, randomized noninferiority trial comparing iron isomaltoside 1000 to iron sucrose over a period of five weeks. Relative response in the iron isomaltoside 1000 group was estimated in the model using a HR of 2.488 over the first five weeks as reported in PROVIDE. No information was included regarding absolute Hb levels or time to symptom improvement.

The health-related quality of life utility value for patients in the responder health state was assumed to be 0.863, the average Canadian (i.e., the general population) utility value reported in Guertin et al. (2018).[2] Nonresponders were assigned a utility of 0.713, based on a disutility of 0.15 reported by Strauss et al. (2018) in US patients with anemia.[3] From week 6 onward, all patients in the model were assigned the utility value of responders (0.863); however, no further treatment costs, such as those associated with re-treatment, were applied.

Cost inputs included the acquisition cost of iron therapy, estimated at $738 for iron isomaltoside 1000 and $423 for iron sucrose, based on the mean received dose for each comparator in the PROVIDE trial of 1,640 mg and 1,128 mg, respectively. The number of infusions required was calculated by dividing the mean dose by the maximum dose per treatment (i.e., 1,000 mg and 200 mg for iron isomaltoside 1000 and iron sucrose, respectively), leading to an estimated 6.0 visits per course of therapy with iron sucrose and 1.6 visits per course with iron isomaltoside 1000. Additional costs included those associated with administration of the infusions, such as nursing time for IV preparation, active infusion surveillance, and post-infusion observation. Costs for infusion accessories included IV devices, catheters, and bandages. There were also the costs of infusion chair time, and laboratory monitoring costs for a complete blood count (CBC) panel and ferritin test with each visit (see Table 10).

Sponsor's Base Case

The sponsor's base-case probabilistic results reported that iron isomaltoside 1000 was associated with cost savings of $570 compared to iron sucrose and 0.0026 additional QALYs, meaning that iron isomaltoside 1000 was dominant over iron sucrose (see Table 2).

Table 2: Sponsor's Probabilistic Base-Case Results

Comparator	Total costs ($)	Incremental cost of iron isomaltoside 1000 ($)	Total QALYs	Incremental QALYs of iron isomaltoside 1000	Incremental cost per QALY
Iron isomaltoside 1000	916.47	(569.51)	0.4364	0.0026	Iron isomaltoside 1000 is dominant
Iron sucrose	1,485.99		0.4338		

QALY = quality-adjusted life-year.

Note: Sponsor initially reported the median probabilistic results; this table reports the mean. Negative numbers (i.e., cost savings) are reported in brackets.

Summary of Sponsor's Sensitivity Analyses

In addition to the perspective of a Canadian publicly funded health care payer, the sponsor conducted an analysis from a societal perspective, where patients were assumed to have a productivity loss of 3.5 hours per infusion visit, for a total of 5.8 hours lost for iron isomaltoside 1000 (assuming 1.6 visits) and 21.1 hours lost for iron sucrose (assuming six visits). When multiplied by the average hourly wage reported by Statistics Canada of $27.69, this led to an additional cost of $161 for iron isomaltoside 1000 and $583 for iron sucrose. Iron isomaltoside 1000 dominated iron sucrose by a wider margin in this analysis.

Two other scenarios were considered by the sponsor, with iron isomaltoside 1000 remaining dominant in both of them:

- No re-treatment occurs and patients who had not responded by week 5 remain with the utility of nonresponders throughout the remaining time horizon.
- Re-treatment with the same therapy was assumed at week 6 for all patients who had not yet responded. The cost of re-treatment was applied, and all patients were assumed to transition to the responder state after a further 4 weeks.

The sponsor also conducted a series of deterministic one-way sensitivity analyses varying the number of visits required for iron sucrose, the number of visits required for iron isomaltoside 1000, the HR for response between iron sucrose and iron isomaltoside 1000, the time of infusion for iron sucrose, the disutility associated with IDA, the cost of infusion chair time, the amount of productivity loss per visit, the average hourly wage of Canadians, the average hourly wage of nurses, and the percentage of their attention nurses need to devote to longer infusions. Iron isomaltoside 1000 remained dominant over iron sucrose in all analyses.

Limitations of Sponsor's Submission

Long-Term Cost-Effectiveness Unknown: The sponsor's model is reported as being six months long; however, all differences in costs and quality of life occur within the first five weeks. Rerunning the sponsor's analysis using only the first five weeks of inputs did not noticeably alter the results. While the sponsor included two scenarios, exploring re-treatment

costs in nonresponders and not equating the utility value of nonresponders to that of responders at week 6, all inputs are based on assumptions rather than informed by re-treatment data. The relative clinical and cost-effectiveness of iron isomaltoside 1000 compared to iron sucrose over a time period longer than five weeks is unknown.

Health States of Uncertain Relevance: The sponsor's assumption that patients who had not responded to either iron isomaltoside 1000 or iron sucrose would have a utility value consistent with IDA, while those whose Hb had improved by at least 2 g/dL would have a utility value consistent with the Canadian average, is overly simplistic. While patients are likely to begin feeling better as Hb levels start to improve, quality of life may depend on their baseline Hb levels as well as their initial increase, and thus be dependent on how close or far they are from being within a normal range. A model that reflects patients moving through various levels of iron deficiency may better represent changing quality of life than a binary model based on a surrogate outcome about preliminary response or lack of response.

Number of Iron Sucrose Infusions Overestimated: Iron sucrose is used off-label in Canada for the broader population of patients with IDA without chronic kidney disease (CKD). Dosing recommendations for iron sucrose for its indicated CKD populations range from 100 mg to 300 mg of iron sucrose being infused at a time (see Table 4). According to the clinical expert consulted by CADTH, iron sucrose is most frequently infused at 300 mg at a time, generally over two hours, in the broader population of patients with IDA who are unresponsive or unable to tolerate oral iron supplementation. The amount of drug administered at each infusion impacts the number of required infusions, with six infusions required to achieve the mean dose of 1,128 mg of iron sucrose administered in the PROVIDE trial if 200 mg are administered at a time, while only four infusions are required if 300 mg are administered at a time. CADTH's base-case analysis therefore considers 300 mg infusions (i.e., four infusions) of iron sucrose to be a more conservative assumption for comparator costs. However, the potential impact of this more rapid dosing on improving time to response with iron sucrose relative to iron isomaltoside 1000 is unknown.

Generalizability of Disutility Is Uncertain: The utility of response was assumed to be that of average Canadian utility (0.863), as reported in Guertin et al. (2018).[2] Based on a study that found that IDA patients in the US reported a utility value of 0.62,[3] and comparing this to the mean utility reported for the general US population (0.75 to 0.80), the sponsor concluded that IDA is associated with a disutility of 0.15. This disutility was applied to the average Canadian utility value to arrive at a utility weight of 0.713 for not responding within the model. However, given the difference between the average Canadian and average American utility score for the general population, as well as uncertainty in generalizability of health preferences between one country and another, the magnitude of the disutility assigned to not responding to therapy is uncertain. CADTH conducted sensitivity analyses around this parameter (see Table 14).

Chronic Iron Supplementation Was Not Considered: The sponsor's model considers only a single course of therapy within the six-month time horizon. However, the expert consulted by CADTH predicts that some patients, such as those with inflammatory bowel disease or severe menorrhagia, would regularly require IV iron supplementation for IDA. CADTH conducted a cost analysis to calculate an annual cost for both iron isomaltoside 1000 and iron sucrose if used in this manner (see Table 15).

Overestimation of Monitoring Costs: The clinical expert consulted by CADTH believed that, unlike in the clinical trial, patients in clinical practice would have their Hb and ferritin levels monitored at regular intervals rather than at every infusion visit. The expert therefore

believed that the number of ferritin and CBC monitoring tests ordered would not differ between treatments. As a result, CADTH included two ferritin tests and CBC panels per patient in the revised base case regardless of treatment received, rather than equating the number of tests with the number of infusion visits.

AEs Not Included: The sponsor did not incorporate AEs into the model. While severe AEs were rare, the type experienced within the trial differed between treatments (severe dyspnea and pruritic rash, moderate syncope for iron isomaltoside 1000 versus severe anaphylactic reaction for iron sucrose) and may require different resources for their management. Patients in the iron isomaltoside 1000 group also reported more skin and subcutaneous tissue disorders as well as hypophosphatemia, while iron sucrose was associated with more nervous system and gastrointestinal disorders. However, it is unlikely this oversight substantially biases results.

Probabilistic Variation Based on Assumption: While most inputs within the sponsor's model were varied probabilistically, a large majority of these inputs had distributions that were bound by varying the mean by 25% rather than being informed by data. Reliance on an assumed variation around the mean to inform an input's distribution reduces the likelihood that the model reflects the true extent of probable outcomes in the real world. Additionally, while the sponsor included variation around the HR linking the efficacy of iron isomaltoside 1000 to that of iron sucrose in the probabilistic analysis, the underlying efficacy of iron sucrose did not itself vary.

CDR Reanalyses

While several limitations with the sponsor's model could not be addressed in the reanalyses (time horizon, AEs, relevance of health states), other limitations could be explored by CADTH, including:

- Laboratory monitoring (CBC panel and ferritin test) is equal between comparators, with two tests per patient.
- A total of 300 mg of iron sucrose is infused per visit, consistent with the assessment of the expert consulted by CADTH on how iron sucrose is typically administered in Canada. This reduces the mean number of infusions for iron sucrose from six to four.
- The limits of the hourly wage for nurses is informed by the minimum and maximum entries for Canada as cited by Statistics Canada, rather than by assuming a 25% variance around the median.

The results from these stepwise analyses can be found in Table 3, culminating in a CADTH base case that found that iron isomaltoside 1000 was associated with 0.0026 additional QALYs at a savings of $148, making iron isomaltoside 1000 dominant over iron sucrose. The model was most sensitive to the assumed dose per infusion of iron sucrose.

Table 3: CADTH Base-Case Reanalyses

	Description	Sponsor's base-case value	CADTH value	Incremental cost ($)	Incremental QALYs	ICUR ($/QALY)
	Sponsor's base case	**Reference**		(569.51)	0.0026	Iron isomaltoside 1000 dominant
1	Equal lab monitoring	Lab tests are run 1.7 times for iron isomaltoside 1000 and 6.0 times for iron sucrose	Lab monitoring occurs twice per patient, regardless of comparator	(447.64)	0.0026	Iron isomaltoside 1000 dominant
2	300 mg iron sucrose per infusion	200 mg iron sucrose administered per infusion (6 visits)	300 mg iron sucrose administered per infusion (4 visits)	(215.92)	0.0026	Iron isomaltoside 1000 dominant
3	Greater variance in nurse wages	Assumes nurse wage varies by 25% around median	Assumes nurse wage is bounded by maximum and minimum rate reported for Canada[a]	(572.24)	0.0026	Iron isomaltoside 1000 dominant
1 to 3	**CADTH base case**			**(148.42)**	**0.0026**	**Iron isomaltoside 1000 dominant**

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

[a] As reported for Independent Practice - Registered Nurse in Canada in the Job Bank database of the Government of Canada.[4]

There is substantial uncertainty in the clinical benefit associated with iron isomaltoside 1000, when compared to that of iron sucrose. While response to iron therapy in terms of Hb level improvement is a reasonable indicator that a patient's quality of life is or will soon improve, the simplistic way quality of life is represented within the model makes the magnitude of benefit difference between comparators uncertain. Additionally, the model uses a disutility for IDA from an American source, which may or may not reflect preferences in the corresponding Canadian population. The impact of the higher doses of iron sucrose with the CADTH base case on time to response is also uncertain; this would likely lower the HR when time to response for iron isomaltoside 1000 is compared to iron sucrose, decreasing the benefit in terms of QALYs gained. However, the magnitude of this is uncertain and thus not considered. Finally, the model does not consider the quality of life or cost impact of AEs associated with either comparator, nor is it clear how many patients will continue to respond after five weeks for the entirety of the six-month time horizon once treatment stops. Taken altogether, it is uncertain whether the very small quality of life benefit associated with iron isomaltoside 1000 when compared to iron sucrose (0.0026 additional QALYs) will in fact be realized.

CADTH conducted scenario analyses considering both a larger (0.20) and smaller (0.10) disutility being associated with the IDA health state, as well as by assuming that there is no efficacy difference (HR = 1), and thus no quality of life difference, between iron isomaltoside 1000 and iron sucrose.

CADTH also considered re-treatment scenarios consistent with the sponsor's scenario 2, where all nonresponders are assumed to be re-treated after six weeks, and assumed to respond a further four weeks later. This analysis increased the dominance of iron isomaltoside 1000 compared to iron sucrose, with a larger QALY benefit and further cost savings. However, without data to inform the relative efficacy of re-treatment or time to response in this scenario, the results are highly uncertain.

The expert consulted by CADTH emphasized that some IDA patients, such as those with inflammatory bowel disease or severe menorrhagia, require long-term or chronic IV iron supplementation rather than a one-time treatment course. While CADTH was unable to conduct a cost-effectiveness analysis due to a lack of comparative data for repeated or chronic use, an example cost comparison over a one-year time horizon is presented in Table 15. Patients in this analysis were assumed to receive 300 mg of iron sucrose over a two-hour infusion every six weeks or 1,000 mg of iron isomaltoside 1000 over a 30-minute infusion every 18 weeks. Laboratory monitoring was not assumed to vary between treatments. Under these assumptions, the use of iron isomaltoside 1000 was associated with an additional $325 in drug acquisition costs, but a savings of $1,061 in administration costs, for a total savings of $736 per patient per year compared to iron sucrose.

Issues for Consideration

Differing Budget Holders: While the use of iron isomaltoside 1000 is associated with overall cost savings compared to iron sucrose from a Canadian publicly funded health care payer perspective due to decreased infusion time and, thus, reduced administration costs, from a public drug plan perspective, iron isomaltoside 1000 is associated with higher drug acquisition costs than iron sucrose (see Table 16). Transitioning from iron sucrose to iron isomaltoside 1000 may therefore be complicated by increased costs for some budget holders (i.e., public drug plans) while the associated savings are seen by others (e.g., hospital budget holders). When considering drug costs alone, the cost of iron isomaltoside 1000 would need to be reduced by 17% to equal that of iron sucrose when considering equivalent doses of elemental iron, and by 43% when considering the mean received doses of each comparator in the PROVIDE trial.

Patient Input

Input was received from Crohn's and Colitis Canada and the Kidney Foundation of Canada. Feedback from the patient groups indicated that IDA is quite common in both patients with inflammatory bowel disease and CKD. Patients described the most common symptoms as weakness, fatigue, low energy, shortness of breath, poor concentration, and compromised quality of life. When choosing iron supplementation therapies, patients indicated they faced trade-offs between oral tablets, which are a more convenient treatment but have a slower response, compared to iron infusions in a clinical setting, which require an appointment and potentially missing school or work hours but come with more immediate results. Patients also expressed concern at the high cost of iron infusions when not reimbursed.

Two patients from Crohn's and Colitis Canada had experience with iron isomaltoside 1000 and expressed that the treatment was easy (compared to iron sucrose with fewer infusions), effective (energy levels returned), and fast (felt better within a few days). One of these patients experienced a burning sensation while being infused, along with skin flushing and heart palpitations; these symptoms resolved with the administration of diphenhydramine and restarting the infusion at a slower speed. The other patient had no adverse effects. See the Stakeholder Engagement section of the *CADTH Common Drug Review Clinical Review Report for Monoferric* (2020) for further details.

Conclusions

After attempting to address several limitations with the sponsor's analysis, where possible, CADTH's base case found that iron isomaltoside 1000 was dominant when compared to iron sucrose, yielding 0.0026 additional QALYs and costing $148 less.

However, a number of limitations could not be addressed, including uncertainty in the relevance of the health states as modelled, the lack of consideration for AEs, the assumed variation in the probabilistic inputs, and the unknown long-term cost-effectiveness of iron isomaltoside 1000 compared to iron sucrose. The 0.0026 QALY benefit associated with iron isomaltoside 1000 is small and uncertain, given these limitations. However, iron isomaltoside 1000 remains less expensive than iron sucrose when total costs are considered, including administration, due to the lower number of required infusions per treatment course.

Appendix 1: Cost Comparison

The comparators presented in the following table have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice, versus actual practice. Comparators are not restricted to drugs but may be devices or procedures. Costs are sponsor list prices, unless otherwise specified. Existing product listing agreements are not reflected in the following table and as such may not represent the actual costs to public drug plans.

Table 4: CDR Cost Comparison Table for Parenteral Iron Products for IDA

Drug/comparator	Strength	Dose form	Price ($)	Recommended dose	Average drug cost per treatment course ($)
Iron isomaltoside 1000 (Monoferric)	1 mL 5 mL 10 mL	100 mg/mL elemental iron, single use solution for IV infusion	45.0000[a] 225.0000[a] 450.0000[a]	*Simplified*[b] Patients < 70 kg • If Hb ≥ 10 g/dL: 1,000 mg • If Hb < 10 g/dL: 1,500 mg Patients ≥ 70 kg • If Hb ≥ 10 g/dL: 1,500 mg • If Hb < 10 g/dL: 2,000 mg	450 to 900
Iron dextran (Dexiron)[c]	2 mL	50 mg/mL elemental iron, single use vial for IV or IM injection	27.5000	Based on patient lean body weight and observed Hb • Adult range: 21 mL to 66 mL[d] 2 mL (100 mg) or less may be given daily until calculated total amount reached	303 to 908
Iron sucrose (Venofer)[e]	5 mL	20 mg/mL elemental iron, single use vials	37.5000	NDD-CKD patients: 1,000 mg cumulative dose, in 5 sessions over a 14-day period HDD-CKD patients: 1,000 mg cumulative dose, 100 mg at a time PDD-CKD patients: 1,000 mg cumulative dose, 2 infusions of 300 mg each 14 days apart, followed by a 400 mg infusion 14 days later	375
Sodium ferric gluconate complex (Ferrlecit)[f]	5 mL	12.5 mg/mL elemental iron, single use vials	26.3600	125 mg (10 mL) per session; most patients will require a minimum cumulative dose of 1,000 mg of elemental iron over 8 sessions at sequential dialysis treatments to achieve response	422 or more

CDR = CADTH Common Drug Review; Hb = hemoglobin; HDD-CKD = hemodialysis-dependent chronic kidney disease; IDA = iron deficiency anemia; IM = intramuscular; NDD-CKD = non–dialysis-dependent chronic kidney disease; PDD-CKD = peritoneal dialysis-dependent chronic kidney disease.

Note: All prices are from the Saskatchewan Drug Plan Formulary (accessed July 2019) unless otherwise indicated and do not include dispensing fees or administration.

[a] Sponsor-submitted price.

[b] Cumulative required dose may also be calculated using the Ganzoni formula; see Table 12.

[c] Indicated for the treatment of patients with documented iron deficiency in whom oral iron administration is unsatisfactory or impossible. Dexiron is listed as to be discontinued according to Drug Shortages Canada,[5] although at the time of this report it was still marketed according to Health Canada.[6] The clinical expert consulted by CADTH did not consider Dexiron to be a key comparator.

[d] Calculated using lean body weight = (45.5 kg for women or 50 kg for men) + 2.3 kg for every 2.5 cm (each inch) of height above 152.4 cm (5 feet) as per product monograph. Range assumes height of between 142 cm tall (4 feet 8 inches) and 193 cm tall (6 feet 4 inches), corresponding to the first (for women) and 99th (for men) percentiles of adult height, with Hb values between 3 g/dL and 10 g/dL. See product monograph for further detail.[7]

[e] Indicated for the treatment of IDA in NDD-CKD patients receiving an erythropoietin or not, and in HDD-CKD and PDD-CKD patients receiving an erythropoietin.

[f] Indicated for the treatment of IDA in patients undergoing chronic hemodialysis who are receiving supplemental erythropoietin therapy. The expert consulted by CADTH did not consider Ferrlecit a key comparator.

Appendix 2: Summary of Key Outcomes

Table 5: When Considering Only Costs, Outcomes, and Quality of Life, how Attractive is IV Iron Isomaltoside 1000 Relative to IV Iron Sucrose?

Iron isomaltoside vs. iron sucrose	Attractive	Slightly attractive	Equally attractive	Slightly unattractive	Unattractive	NA
Costs (total)		X				
Drug treatment costs alone				X		
Clinical outcomes			X			
Quality of life			X			
Incremental CE ratio or net benefit calculation	Iron isomaltoside 1000 is dominant over iron sucrose.					

CE = cost-effectiveness; NA = not applicable; vs. = versus.

Appendix 3: Additional Information

Table 6: Submission Quality

	Yes/ good	Somewhat/ average	No/ poor
Are the methods and analysis clear and transparent?	X		
Comments Reviewer to provide comments if checking “no”	None		
Was the material included (content) sufficient?	X		
Comments Reviewer to provide comments if checking “poor”	None		
Was the submission well organized and was information easy to locate?	X		
Comments Reviewer to provide comments if checking “poor”	None		

Table 7: Authors Information

Authors of the pharmacoeconomic evaluation submitted to CADTH

☐ Adaptation of global model/Canadian model done by the sponsor

☐ Adaptation of global model/Canadian model done by a private consultant contracted by the sponsor

☐ Adaptation of global model/Canadian model done by an academic consultant contracted by the sponsor

☒ Other (de novo model)

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document			X
Authors had independent control over the methods and right to publish analysis			X

Appendix 4: Summary of Other Health Technology Assessment Reviews of Drug

Three other health technology assessment agencies have reviewed iron isomaltoside 1000 for the treatment of IDA: the Institut national d'excellence en santé et en services sociaux (Quebec) in 2018, the Pharmaceutical Benefits Advisory Committee (Australia), also in 2018, and the Scottish Medicines Consortium (Scotland) in 2011. A summary of the pharmacoeconomic submissions and recommendations for iron isomaltoside 1000 from these agencies can be found in Table 8.

Table 8: Other Health Technology Assessment Findings

	INESSS (September 2018)[a]	PBAC (July 2018)[b]	SMC (April 2011)[c]
Treatment	Iron isomaltoside 1000, 100 mg/mL (Monoferric)	Ferric derisomaltose, 100 mg/mL (Monofer)[d]	Iron isomaltoside 1000, 100 mg/mL (Monofer)
Price	$45.00 per 1 mL $225.00 per 5 mL $450.00 per 10 mL	AU$307.49 for 2 vials of 5 mL each (CA$277; exchange rate: AU$1.00 = CA$0.9022)[11]	Cost per tx ~ £170 to £237 (CA$278 to $387; exchange rate: UK pound sterling £1.00 = CA$1.6330)[11]
Similarities with CADTH submission	Comparison vs. iron sucrose: Included drug acquisition, preparation, administration, monitoring costs, and lost productivity for societal perspective	Few	Costs include nursing time and consumable costs
Differences with CADTH submission	CMA assuming equal efficacy, societal perspective	CMA vs. ferric carboxymaltose: Assumed equivalent dosing at doses > 1,000 mg ferric derisomaltose involved fewer infusions. Equal efficacy based on noninferiority trials and indirect comparison	CMA vs. iron sucrose, iron dextran, ferric carboxymaltose, and blood transfusions in non–dialysis-dependent patients. Costs included patient transportation
Sponsor's results	Redacted	Sponsor set cost of ferric derisomaltose same as ferric carboxymaltose — thus, cost-neutral at a 1:1 equi-effective dose	Savings ~ £85 to £142 (CA$139 to $232) per 1,000 mg tx course vs. iron sucrose and £24 (CA$39) vs. iron dextran.[11] Savings were also estimated but not reported for iron isomaltoside 1000 vs. ferric carboxymalrose and blood transfusions
Issues noted by the review group	• Dose for each comparator changed from equi-dosing to mean doses in PROVIDE • Number of visits/patient was changed to be consistent with means in PROVIDE • Lost productivity was changed to half day per visit/patient to account for travel time + administration time • Concluded administration was similar for hemodialysis patients for iron isomaltoside 1000 and other products — thus, more	• Noted that PROVIDE had average dose of 1,640 mg, leading to cost of AU$614.98 per course (CA$555)[11] • Maximum dose of ferric derisomaltose is 1,500 mg vs. 1,000 mg for ferric carboxymaltose — thus, listing former may result in an increase in prescribed dose overall and an increase in cost/patient	• Cost savings from nursing time overstated; 1,000 mg of iron isomaltoside 1000 were cost savings vs. 1,000 mg iron sucrose, assuming 50% of patients required transport; more expensive vs. 1,000 mg iron dextran • Lack of evidence to establish relevant average comparator dose • Infusion time for iron dextran overestimated • Cost-effectiveness when iron isomaltoside 1000 given as an IV bolus is unknown

	INESSS (September 2018)[a]	PBAC (July 2018)[b]	SMC (April 2011)[c]
	expensive iron isomaltoside 1000 not an efficient option		
Results of reanalyses by the review group (if any)	Average cost per tx course/patient not undergoing hemodialysis was $959 for iron isomaltoside 1000 and $1,132 for iron sucrose, a savings of $173	Redacted; cost per 1,000 mg was AU$307.49 (CA$277)[11]	Iron isomaltoside 1000 cost £170 to £237 (CA$278 to $387) per tx while ferric carboxymaltose cost £191 (CA$311) and iron dextran cost £80 to £112 (CA$131 to $183)[11]
Recommendation	Recommended to reimburse for the tx of iron deficiency anemia	Recommended to list as an unrestricted benefit for the tx of iron deficiency anemia when oral iron is ineffective or not tolerated	Recommended with conditions: • When oral iron is ineffective or cannot be used • Where there is clinical need to deliver iron rapidly Use was restricted to administration by high dose infusion and excluded use in patients receiving hemodialysis

CMA = cost-minimization analysis; INESSS = Institut national d'excellence en santé et en services sociaux; PBAC = Pharmaceutical Benefits Advisory Committee; SMC = Scottish Medicines Consortium; tx = treatment; vs. = versus.

[a] Institut national d'excellence en santé et en services sociaux, avis transmis au ministre for Monoferric.[8]

[b] Pharmaceutical Benefits Advisory Committee, Public Summary Document: Monofer.[9]

[c] Scottish Medicines Consortium, advice on Monofer.[10]

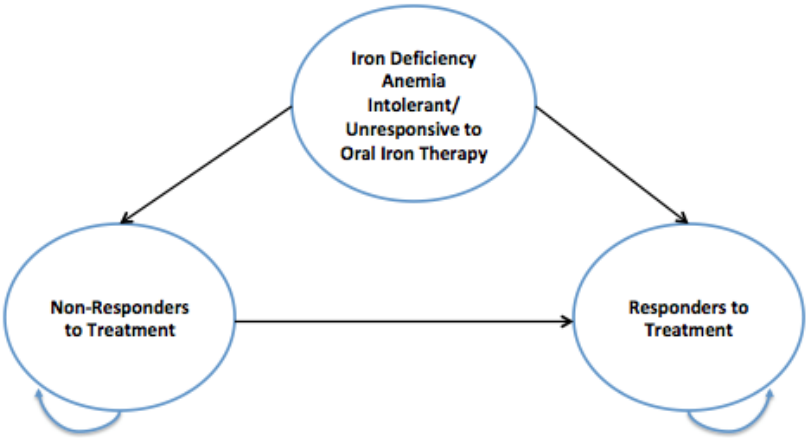
[d] Iron isomaltoside 1000 and ferric derisomaltose are alternate chemical names for the same medication.

Appendix 5: Reviewer Worksheets

Sponsor's Model Structure

The sponsor submitted a state-transition model comparing iron isomaltoside 1000 (Monoferric) to iron sucrose (Venofer) for the treatment of adult patients with IDA who have intolerance or unresponsiveness to oral iron therapy. The base case was a probabilistic model of 5,000 iterations over a six-month time horizon, with transitions possible during each of the first five weeks. No discounts were applied to costs or outcomes, nor was mortality applied, given the short time horizon. Patients enter the model in an IDA health state and, at the end of the first cycle, transition into either a responder health state or a nonresponder health state. Thereafter, responder patients remain in the responder state while nonresponders may either remain as nonresponders or switch to the responder state at the end of each of the first five cycles (see Figure 1).

Figure 1: Model Structure Overview



Source: Sponsor's pharmacoeconomic submission.

Efficacy within the model was based on time to response within the PROVIDE trial, which compared iron isomaltoside 1000 to iron sucrose, with response being defined as an Hb increase of at least 2 g/dL. The proportion of patients who have responded by each week is outlined in Table 9, with the model being based on the Kaplan–Meier time to response curve for iron sucrose, and the HR calculated within the trial for iron isomaltoside 1000.

Table 9: Model Efficacy Input: Percentage Responders at Each Time Point for Iron Sucrose and Iron Isomaltoside 1000 — Hb Increase of 2 g/dL or More

Week	Iron sucrose based on trial Kaplan–Meier (%)[a]	Iron isomaltoside based on trial Kaplan–Meier (%)[a]	Iron isomaltoside 1000 based on trial HR (%)[a]
1	0.13	2.14	0.33
2	5.12	30.47	12.25
3	18.35	46.72	39.62
4	35.61	57.14	66.56
5	43.61	67.16	75.96

Hb = hemoglobin; HR = hazard ratio.

Source: Sponsor's pharmacoeconomic submission, Table 4.

[a] PROVIDE trial.[1]

The number of visits per course of therapy was calculated by dividing the mean received dose from the PROVIDE trial[1] (1,640 mg for iron isomaltoside 1000 and 1,128 mg for iron sucrose) by the maximum dose assumed per administration (defined as 1,000 mg for iron isomaltoside 1000 and 200 mg for iron sucrose). This resulted in 1.7 visits per course of therapy for iron isomaltoside 1000 and 6.0 visits for iron sucrose. Infusion costs per visit and per course, as well as incremental costs, are outlined in Table 10.

Table 10: Sponsor's Calculated Infusion Costs

Cost	Iron sucrose cost per visit	Iron isomaltoside 1000 cost per visit	Total iron sucrose cost (6.0 visits)	Total iron isomaltoside 1000 cost (1.7 visits)	Cost difference per therapy course
Nurse cost per visit ($37/hour)	$34.23 (based on 55.5 minutes)[a]	$28.31 (based on 45.9 minutes)[b]	$205.38	$48.13	$157.25
Infusion devices per visit (needle device, IV catheter, bandage)	$7.94	$7.94	$47.64	$13.50	$34.14
Chair time ($0.71/ minute)[c]	$106.50 (based on 150 minutes)	$42.60 (based on 60 minutes)	$639.00	$72.42	$566.58
Laboratory monitoring (CBC panel, ferritin)	$28.47	$28.47	$170.82	$48.40	$122.42
Total administration costs	**$177.14**	**$107.32**	**$1,062.84**	**$182.45**	**$880.39**

CBC = complete blood count.

[a] Includes six minutes for IV preparation, 33% attention for 120 minutes of active infusion surveillance, and 33% attention for 30 minutes of post-infusion observation.[13]

[b] Includes six minutes for IV preparation, 100% attention for 30 minutes of active infusion surveillance, and 33% attention for 30 minutes of post-infusion observation.[13]

[c] Pettigrew et al. (2016).[12]

Source: Sponsor's pharmacoeconomic submission, tables 10, 11, 12, 13, and 14.

Table 11: Data Sources

Data input	Description of data source	Comment
Baseline characteristics	Baseline characteristics of patients not included in model	Unknown if a differential efficacy or side effect profile exists within different patient populations
Efficacy	Proportions of patients responding (Hb increase of at least 2 g/dL) in each of the first 5 weeks were based on the Kaplan–Maier curve from PROVIDE for iron sucrose, with the HR for time to Hb increase relative to iron sucrose used to inform the efficacy of iron isomaltoside 1000.[a] The HR varies in the probabilistic analysis, but the underlying efficacy of iron sucrose does not.	The use of the HR for responding to iron isomaltoside 1000 relative to iron sucrose reported in the PROVIDE trial rather than the directly measured proportion of responders at each time point did not impact results due to the simplistic nature of the model and the short time horizon. It is unclear what impact this approach would have if data over a longer term was available.
Natural history	Limited due to short time horizon and patients' iron deficiency resolving after treatment. All patients were assumed to revert to average Canadian utility (consistent with responder utility) after week 5. Patients are assumed to maintain response for the remainder of the modelled time horizon.	The clinical expert consulted by CADTH suggested that many patients requiring IV iron supplementation use it chronically for conditions such as severe menorrhagia or inflammatory bowel disease. Quality of life differences seen within the model are unlikely to be multiplied across a longer time horizon, as anemia should be manageable with chronic use of either treatment. However, the cost savings in terms of administration time and resources will continue to be saved with less frequent infusions for iron isomaltoside 1000.
Utilities	Utility of response assumed the same as average Canadian utility, as reported in Guertin et al. (2018).[b] Nonresponse was assigned a utility consistent with a 0.15 disutility for iron deficiency anemia found in American patients.[c]	Absolute value of utilities used appears acceptable but disutility may not reflect Canadian preferences, especially considering that mean health utility within each general population is different. Alternate disutility assumptions were explored in CADTH scenario analyses.
AEs	Deemed not relevant as both treatments were well tolerated in the PROVIDE trial with similar results in that 0.6% of patients in both groups experiencing an SAE.	Inappropriate. 22.5% of patients in PROVIDE using iron isomaltoside 1000 and 17.3% using iron sucrose experienced an AE. SAEs were equal between groups (0.6%) but differed in type with iron isomaltoside 1000 patients experiencing severe dyspnea, severe pruritic rash, and moderate syncope, while there were severe anaphylactic reactions in the iron sucrose group. These differences may lead to differing quality of life and resource costs until the AEs subside.
Mortality	Not included due to short time horizon and limited impact of condition.	Acceptable.
Resource use and costs		
Drug	Mean received dose and standard deviation from PROVIDE were used to establish per course drug cost. Sponsor provided costs for iron isomaltoside 1000; iron sucrose price cited as Delta PA price for Ontario, which matches Saskatchewan formulary price Mean doses from PROVIDE trial were used to inform dose within the model. A dose of 1,000 mg was assumed per infusion for iron isomaltoside 1000 and 200 mg per infusion for iron sucrose.	Appropriate. Dosing will vary by patient in clinical practice, particularly if Ganzoni formula is used rather than the simplified table as in the trial; however, means in terms of drug costs are likely to remain similar to clinical trial dose due to wastage of additional medication in vials and physician dose rounding. Appropriate to use the same total dosing that efficacy is based on. Appropriate for iron isomaltoside 1000. However, according to the clinical expert consulted by CADTH, patients are typically given 300 mg of iron sucrose

Data input	Description of data source	Comment
		per infusion, reducing to 200 mg or less only in the case of intolerance, skin reaction, or other AE. Assuming 200 mg per infusion overestimates the likely total infusion costs of iron sucrose in clinical practice.
Administration	Iron isomaltoside 1000 assumed to be infused over 30 minutes, with iron sucrose given over 120 minutes. Infusion device costs and chair time are from Canadian sources. Chair time is derived from a study on overhead costs for chemotherapy infusion.[d] Nurse hourly wage was the Canada-wide median from Government of Canada wage report. The nurse attention proportion is from a costing study on IV iron infusions.[e]	Questionable. The PROVIDE trial infused iron isomaltoside 1000 over 15 minutes and iron sucrose over 30 minutes. However, the clinical expert consulted by CADTH agreed that iron sucrose is typically infused over a period of 120 minutes, and that it was likely that iron isomaltoside 1000 would be infused over 30 minutes. Acceptable. Ideally, chair time cost would be sourced for the same condition to which it is applied; however, the proxy is unlikely to be substantially different. Acceptable for use as a point estimate. Distribution should be bounded by minimum and maximum from same source rather than 25% assumption.
Laboratory monitoring	A ferritin test and CBC panel were assumed to occur at each infusion visit. Costs for tests were sourced from Ontario's *Schedule of Benefits for Laboratory Services*.	Cost source is appropriate but while the clinical expert consulted by CADTH confirmed the types of tests were appropriate, they did not think timing and number of tests ordered would differ between treatments.
Event		
AEs	Not included in model due to low proportion of SAEs in the PROVIDE trial that was similar between groups (0.6%).	Inappropriate. While severe AEs were rare, the type experienced within the trial differed (severe dyspnea and pruritic rash, moderate syncope versus severe anaphylactic reaction) and may require different resources to manage. Patients in the iron isomaltoside 1000 group also reported more skin and subcutaneous tissue disorders as well as hypophosphatemia, while iron sucrose was associated with more nervous system and gastrointestinal disorders. However, barring longer term data with more events, these differences are unlikely to have a substantial impact on the model results.
Health state	Health states accumulated no costs or resource use other than those described above.	Acceptable given nature of condition.

AE = adverse event; CBC = complete blood count; CDR = CADTH Common Drug Review; Hb = hemoglobin; HR = hazard ratio; SAE = serious adverse event.

[a] PROVIDE trial.[1]

[b] Guertin et al. (2018).[2]

[c] Strauss et al. (2018).[3]

[d] Pettigrew et al. (2016).[12]

[e] Bhandari, (2011).[13,14]

Table 12: Ganzoni Formula for Iron Isomaltoside 1000 Dosing

Description	Result
Ganzoni formula	Iron need (mg iron) = body weight (kg)[a] × (target Hb[b] – actual Hb) × 2.4[c] + depot iron need (mg iron)[d]
Example patient	
50 kg patient Actual Hb = 11 10 mg/kg assumption for iron stores	Iron need = 50 × (15 – 11) × 2.4 + (10 × 50) Iron need = 980 mg
70 kg patient Actual Hb = 9 1,000 mg assumption for iron stores	Iron need = 70 × (15 – 9) × 2.4 + 1,000 Iron need = 2,008 mg
90 kg patient Actual Hb =10 1,000 mg/kg assumption for iron stores	Iron need = 90 × (15 – 10) × 2.4 + 1,000 Iron need = 2,080 mg

BMI = body mass index; Hb = hemoglobin.

[a] Ideal body weight should be used for obese patients, e.g., by calculating weight at BMI.
[b] Default target Hb is 15 g/dL. Lower Hb targets may be appropriate based on clinical judgment.

[c] 2.4 = 0.0034 × 0.07 × 10,000, where 0.0034 is the iron content of Hb, 0.07 is blood volume based on 7% of body weight, and 10,000 is the conversion factor from g/dL to mg/L.
[d] For patients above 35 kg, iron stores are at least 500 mg, the lower limit of normal for small women. Some guidelines use 10 mg to 15 mg iron/kg body weight while others use 1,000 mg iron for stores.

Table 13: Sponsor's Key Assumptions

Assumption	Comment
Health state based on response defined as a gain of at least 2 g/dL Hb rather than on absolute Hb level	Questionable. While an Hb increase of 2 g/dL is a good indicator that patient iron levels are improving, it remains a surrogate outcome in terms of quality of life. Health utility would likely to be better modelled to reflect absolute Hb levels approaching the normal range rather than assumed to improve with any gain regardless of baseline value. While utilities based on absolute iron level were not identified, it remains a limitation of the analysis.
Iron deficiency modelled as a 1-time treatment and response	While some patients will receive only a single treatment course with an IV iron supplement, the clinical expert consulted by CADTH considered that there is a substantial population of patients who use IV iron supplementation chronically, such as IBD patients and those with severe menorrhagia.
Patients do not lose response after responding	Appropriate within the 5 weeks of trial data; however, it is unclear what proportion of patients will continue to have improved Hb levels over the model's extension to 6 months vs. those who will require subsequent treatments even after initially responding.
Nonresponders assumed to have general population utility after 5 weeks	Inappropriate. Model should consider response rates over a longer time and consequences of not responding or needing re-treatment before response. The second of the sponsor's scenario analyses attempts to account for re-treatment but is based on assumptions rather than being informed by data.
Iron sucrose assumed to be used in general IDA population rather than only within the indicated chronic kidney disease population	Appropriate. Wider usage was confirmed by the clinical expert consulted by CADTH.
Iron dextran (Dexiron) excluded as a comparator due to impending discontinuation	Acceptable. Dexiron was still reported as marketed by Health Canada in September 2019; however, the anticipated discontinuation date was listed as August 23, 2019, by Drug Shortages Canada.[5] The clinical expert consulted by CADTH did not believe iron dextran to be a significant comparator of interest.
Oral iron supplements were not considered as a comparator	Acceptable. The Health Canada indication for iron isomaltoside 1000 is limited to patients who are unresponsive or unable to tolerate oral iron. Patient input indicates there may be some cases where a choice is presented to patients.

Assumption	Comment
IDA in Canada is associated with the same utility decrement as reported in the US	Acceptable in the absence of Canadian data. Values on either side of a 0.15 disutility (0.10 and 0.20) were tested in CADTH's sensitivity analyses.

Hb = hemoglobin; IBD = inflammatory bowel disease; IDA = iron deficiency anemia; vs. = versus.

Sponsor's Results

The sponsor's base-case analysis results can be found in Table 2.

While all of the deterministic one-way sensitivity analyses described in the main body of this report resulted in iron isomaltoside 1000 remaining dominant over iron sucrose, the greatest difference in costs was seen while varying the number of infusion visits required for iron sucrose, varying the HR describing the relative effectiveness between comparators, varying the infusion time of iron sucrose, varying the disutility associated with IDA, and varying the cost associated per minute of infusion chair time.

CADTH Reanalyses

CADTH's base-case analysis is outlined in Table 3. Scenario analyses exploring uncertainty in the disutility assigned to the IDA health state, as well as assuming equal efficacy between iron isomaltoside 1000 and iron sucrose, can be found in Table 14.

Table 14: CADTH Scenario Analyses Around Base Case

	Description	CADTH base-case value	Scenario value	Incremental cost ($)	Incremental QALYs	ICUR ($/QALY)
	CADTH base case	**Reference**		(148.42)	0.0026	Iron isomaltoside 1000 dominant
A	Lower disutility for IDA	Disutility associated with nonresponse is 0.15	Disutility associated with nonresponse is 0.10	(146.76)	0.0018	Iron isomaltoside 1000 dominant
B	Higher disutility for IDA	Disutility associated with nonresponse is 0.15	Disutility associated with nonresponse is 0.20	(145.54)	0.0035	Iron isomaltoside 1000 dominant
C	Equal efficacy between comparators	HR for time to response is 2.488 for iron isomaltoside 1000 vs. iron sucrose	HR for time to response is 1.000 for iron isomaltoside 1000 vs. iron sucrose	(150.64)	0.000	Iron isomaltoside 1000 is cost saving

HR = hazard ratio; ICUR = incremental cost-utility ratio; IDA = iron deficiency anemia; QALY = quality-adjusted life-year; vs. = versus.

The sponsor's base case and scenario analyses, as well as the CADTH base case and scenario analyses, were all conducted to explore the cost-effectiveness of iron isomaltoside 1000 compared to iron sucrose over a single treatment course, albeit with the potential for re-treatment in some scenarios. However, the clinical expert consulted by CADTH indicated that patients with some conditions, such as inflammatory bowel disease or severe menorrhagia, may receive IV iron supplementation on a more long-term or chronic basis. Insufficient information was available to conduct a CUA comparing iron isomaltoside 1000 to iron sucrose for regular or chronic use. However, a cost comparison is presented in Table 15 that estimates the relative costs of treating patients with 1,000 mg of iron isomaltoside 1000 every 18 weeks, compared with 300 mg of iron sucrose every six weeks. Assuming

resource use similar to those listed in the CUAs described previously, iron isomaltoside 1000 would be associated with an additional $325 per patient per year in drug acquisition costs compared to iron sucrose. However, when administration costs are factored in, iron isomaltoside 1000 would cost an estimated $736 less per patient per year.

Table 15: CDR Cost Comparison for Annual Cost of Chronic IV Iron Supplementation

Cost	Iron sucrose 300 mg cost per visit	Iron isomaltoside 1000 mg cost per visit	Total iron sucrose cost (8.67 visits annually)	Total iron isomaltoside 1000 cost (2.89 visits annually)	Annual incremental cost (savings) with iron Isomaltoside 1000
Drug acquisition costs					
Drug costs	**$112.50**	**$450.00**	**$975.00**	**$1,300.00**	**$325.00**
Administration costs					
Nurse cost ($37/hour)	$34.23 (based on 55.5 minutes)[a]	$28.31 (based on 45.9 minutes)[b]	$296.62	$81.77	($214.85)
Infusion devices per visit (needle device, IV catheter, bandage)	$7.94	$7.94	$68.82	$22.94	($45.88)
Chair time ($0.71/minute)[c]	$106.50 (based on 150 minutes)	$42.60 (based on 60 minutes)	$923.00	$123.07	($799.93)
Laboratory monitoring (CBC panel, ferritin), assumed q.18.w. for both comparators	$28.47	$28.47	$82.25	$82.25	$0
Total administration costs	**$177.14**	**$107.32**	**$1,288.43**	**$227.78**	**($1,060.66)**
Total costs					
Total drug, administration, and monitoring costs	**$261.17**	**$528.85**	**$2,263.43**	**$1,527.78**	**($735.66)**

CBC = complete blood count; CDR = CADTH Common Drug Review; q.18.w. = every 18 weeks.

Note: As per the clinical expert consulted by CADTH, assumes 300 mg iron sucrose infusion every 6 weeks (52 weeks ÷ 6 weeks = 8.67 infusions/year) and 1,000 mg iron isomaltoside 1000 every 18 weeks (52 weeks ÷ 18 weeks = 2.89 infusions/year).

[a] Includes six minutes for IV preparation, 33% attention for 120 minutes of active infusion surveillance, and 33% attention for 30 minutes of post-infusion observation.[13]

[b] Includes six minutes for IV preparation, 100% attention for 30 minutes of active infusion surveillance, and 33% attention for 30 minutes of post-infusion observation.[13]

[c] Pettigrew et al. (2016).[12]

As seen in the previous analyses, from the perspective of a Canadian public drug plan payer, when considering drug costs alone, iron isomaltoside 1000 is more expensive than iron sucrose both when equivalent total doses of elemental iron are considered, as well as when considering the mean doses received by patients in the PROVIDE trial.[1] In order for the drug acquisition cost of iron isomaltoside 1000 to be cost-neutral to that of iron sucrose, the price of iron isomaltoside 1000 would need to be reduced by 17% at equal total doses of elemental iron, or by 43% on the basis of the doses received by patients in the PROVIDE trial.

Table 16: Price Reduction Required for Iron Isomaltoside 1000 to Equal Drug Acquisition Cost of Iron Sucrose

Cost	Cost per mg	Dose considered	Cost per dose	Price reduction for cost-neutrality
Per milligram of elemental iron				
Iron isomaltoside 1000	$0.4500	1,000 mg	$450	16.7%
Iron sucrose	$0.3750	1,000 mg	$375	Reference
Per mean dose received in PROVIDE trial[a]				
Iron isomaltoside 1000	$0.4500	1,640 mg	$738	42.7%
Iron sucrose	$0.3750	1,128 mg	$423	Reference

[a] PROVIDE trial.[1]

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